

WHAT IS CLAIMED IS:

1. A method of reducing extracellular brain glutamate levels, the method comprising administering to a subject in need thereof a therapeutically effective amount of an agent capable of reducing blood glutamate levels thereby reducing extracellular brain glutamate levels.

2. The method of claim 1, wherein said agent is at least one glutamate modifying enzyme and/or a modification thereof.

3. The method of claim 2, wherein said at least one glutamate modifying enzyme is selected from the group consisting of a transaminase, a dehydrogenase, a decarboxylase, a ligase, an aminomutase, a racemase and a transferase.

4. The method of claim 3, wherein said transaminase is selected from the group consisting of glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, acetylornithine transaminase, ornithine-oxo-acid transaminase, succinyldiaminopimelate transaminase, 4-aminobutyrate transaminase, (s)-3-amino-2-methylpropionate transaminase, 4-hydroxyglutamate transaminase, diiodotyrosine transaminase, thyroid-hormone transaminase, tryptophan transaminase, diamine transaminase, cysteine transaminase, L-Lysine 6-transaminase, histidine transaminase, 2-aminoadipate transaminase, glycine transaminase, branched-chain-amino-acid transaminase, 5-aminovalerate transaminase, dihydroxyphenylalanine transaminase, tyrosine transaminase, phosphoserine transaminase, taurine transaminase, aromatic-amino-acid transaminase, aromatic-amino-acid-glyoxylate transaminase, leucine transaminase, 2-aminohexanoate transaminase, ornithine(lysine) transaminase, kynurenine-oxoglutarate transaminase, D-4-hydroxyphenylglycine transaminase, cysteine-conjugate transaminase, 2,5-diaminovalerate transaminase, histidinol-phosphate transaminase, diaminobutyrate-2-oxoglutarate transaminase, and udp-2-acetamido-4-amino-2,4,6-trideoxyglucose transaminase.

5. The method of claim 3, wherein said dehydrogenase is a glutamate

dehydrogenase.

6. The method of claim 3, wherein said decarboxylase is a glutamate decarboxylase.

7. The method of claim 3, wherein said ligase is a glutamate-ethylamine ligase.

8. The method of claim 3, wherein said transferase is selected from the group consisting of glutamate N-acetyltransferase and adenylyltransferase.

9. The method of claim 3, wherein said aminomutase is a glutamate-1-semialdehyde 2,1-aminomutase.

10. The method of claim 1, wherein said agent is at least one co-factor of a glutamate modifying enzyme.

11. The method of claim 10, wherein said co-factor is selected from the group consisting of oxaloacetate, pyruvate, NAD^+ , NADP^+ , 2-oxohexanedioic acid, 2-oxo-3-sulfopropionate, 2-oxo-3-sulfinopropionic acid, 2-oxo-3-phenylpropionic acid, 3-indole-2-oxopropionic acid, 3-(4-hydroxyphenyl)-2-oxopropionic acid, 4-methylsulfonyl-2-oxobutyric acid, 3-hydroxy-2-oxopropionic acid, 5-oxopentanoate, 6-oxo-hexanoate, glyoxalate, 4-oxobutanoate, α -ketoisocaproate, α -ketoisovalerate, α -keto- β -methylvalerate, succinic semialdehyde-(-4-oxobutyrate), pyridoxal phosphate, pyridoxal phosphate precursors and 3-oxoisobutanoate.

12. The method of claim 1, wherein said agent is a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate and/or a modification thereof.

13. The method of claim 12, wherein said modified glutamate converting enzyme is modified human GOT.

14. The method of claim 1, wherein said agent is a co-factor of a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate.

15. The method of claim 14, wherein said agent is selected from the group consisting of lipoic acid, lipoic acid precursor, pyridoxal phosphate, pyridoxal phosphate precursor, thiamine pyrophosphate and thiamine pyrophosphate precursor.

16. The method of claim 1, wherein said agent includes a glutamate modifying enzyme and a co-factor thereof.

17. The method of claim 1, wherein said agent includes a glutamate modifying enzyme and a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate.

18. The method of claim 1, wherein said agent includes a co-factor of a glutamate modifying enzyme and a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate.

19. The method of claim 1, wherein said agent includes a co-factor of a glutamate modifying enzyme, a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate and a co-factor thereof.

20. The method of claim 1, wherein said agent includes a glutamate modifying enzyme, a co-factor thereof, a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate and a co-factor thereof.

21. The method of claim 1, wherein said agent includes a glutamate modifying enzyme, a co-factor thereof, and a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate.

22. The method of claim 1, wherein said agent includes a glutamate modifying enzyme, a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate and a co-factor thereof.

23. The method of claim 1, wherein said agent includes a glutamate modifying enzyme and a co-factor of a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate.

24. The method of claim 1, wherein said agent includes a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate and a co-factor thereof.

25. The method of claim 1, wherein said agent includes a co-factor of a glutamate modifying enzyme and a co-factor of a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate.

26. The method of claim 1, wherein said administering is effected at a concentration of said agent not exceeding 1 g/Kg body weight/hour.

27. The method of claim 1, wherein said agent is at least one inhibitor of a glutamate synthesizing enzyme.

28. The method of claim 27, wherein said inhibitor is selected from the group consisting of gamma-Acetylenic GABA, GABAculine, L-canaline, 2-amino-4-(aminooxy)-n-butanoic acid, 3-Chloro-4-aminobutanoate, 3-Phenyl-4-aminobutanoate, Isonicotinic hydrazide;(S)-3-Amino-2-methylpropanoate, Phenylhydrazine; 4-Fluorophenyl)alanine, Adipate, Azaleic acid, Caproate, 3-Methylglutarate, Dimethylglutarate, Diethylglutarate, Pimelate, 2-Oxoglutamate, 3-Methyl-2-benzothiazolone hydrazone hydrochloride, Phenylpyruvate, 4-hydroxyphenylpyruvate, Prephenate and Indole pyruvate.

29. A pharmaceutical composition for reducing extracellular brain glutamate levels, the pharmaceutical composition comprising, as an active ingredient, an agent capable of reducing blood glutamate levels and a pharmaceutically acceptable carrier.

30. The pharmaceutical composition of claim 29, wherein said agent is at least one glutamate modifying enzyme and/or a modification thereof.

31. The pharmaceutical composition of claim 30, wherein said at least one glutamate modifying enzyme is selected from the group consisting of a transaminase, a dehydrogenase, a decarboxylase, a ligase, an aminomutase, a racemase and a transferase.

32. The pharmaceutical composition of claim 31, wherein said transaminase is selected from the group consisting of glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, acetylornithine transaminase, ornithine-oxo-acid transaminase, succinyldiaminopimelate transaminase, 4-aminobutyrate transaminase, (s)-3-amino-2-methylpropionate transaminase, 4-hydroxyglutamate transaminase, diiodotyrosine transaminase, thyroid-hormone transaminase, tryptophan transaminase, diamine transaminase, cysteine transaminase, L-Lysine 6-transaminase, histidine transaminase, 2-aminoadipate transaminase, glycine transaminase, branched-chain-amino-acid transaminase, 5-aminovalerate transaminase, dihydroxyphenylalanine transaminase, tyrosine transaminase, phosphoserine transaminase, taurine transaminase, aromatic-amino-acid transaminase, aromatic-amino-acid-glyoxylate transaminase, leucine transaminase, 2-aminohexanoate transaminase, ornithine(lysine) transaminase, kynurenine-oxoglutarate transaminase, D-4-hydroxyphenylglycine transaminase, cysteine-conjugate transaminase, 2,5-diaminovalerate transaminase, histidinol-phosphate transaminase, diaminobutyrate-2-oxoglutarate transaminase, udp-2-acetamido-4-amino-2,4,6-trideoxyglucose transaminase.

33. The pharmaceutical composition of claim 31, wherein said

dehydrogenase is a glutamate dehydrogenase.

34. The pharmaceutical composition of claim 31, wherein said decarboxylase is a glutamate decarboxylase.

35. The pharmaceutical composition of claim 31, wherein said ligase is a glutamate-ethylamine ligase.

36. The pharmaceutical composition of claim 31, wherein said transferase is selected from the group consisting of glutamate N-acetyltransferase and adenylyltransferase.

37. The pharmaceutical composition of claim 31, wherein said aminomutase is a glutamate-1-semialdehyde 2,1-aminomutase.

38. The pharmaceutical composition of claim 29, wherein said agent is at least one co-factor of a glutamate modifying enzyme.

39. The pharmaceutical composition of claim 38, wherein said co-factor is selected from the group consisting of oxaloacetate, pyruvate, NAD^+ , NADP^+ , 2-oxohexanedioic acid, 2-oxo-3-sulfopropionate, 2-oxo-3-sulfinopropionic acid, 2-oxo-3-phenylpropionic acid, 3-indole-2-oxopropionic acid, 3-(4-hydroxyphenyl)-2-oxopropionic acid, 4-methylsulfonyl-2-oxobutyric acid, 3-hydroxy-2-oxopropionic acid, 5-oxopentanoate, 6-oxo-hexanoate, glyoxalate, 4-oxobutanoate, α -ketoisocaproate, α -ketoisovalerate, α -keto- β -methylvalerate, succinic semialdehyde-(-4-oxobutyrate), pyridoxal phosphate, pyridoxal phosphate precursor and 3-oxoisobutanoate.

40. The pharmaceutical composition of claim 29, wherein said agent is a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate and/or a modification thereof.

41. The pharmaceutical composition of claim 40, wherein said modified glutamate converting enzyme is a modified GOT.

42. The pharmaceutical composition of claim 29, wherein said agent is a co-factor of a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate.

43. The pharmaceutical composition of claim 42, wherein said agent is selected from the group consisting of lipoic acid, lipoic acid precursor, pyridoxal phosphate, pyridoxal phosphate precursor, thiamine pyrophosphate and thiamine pyrophosphate precursor.

44. The pharmaceutical composition of claim 29, wherein said agent includes a glutamate modifying enzyme and a co-factor thereof.

45. The pharmaceutical composition of claim 29, wherein said agent includes a glutamate modifying enzyme and a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate.

46. The pharmaceutical composition of claim 29, wherein said agent includes a co-factor of a glutamate modifying enzyme and a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate.

47. The pharmaceutical composition of claim 29, wherein said agent includes a co-factor of a glutamate modifying enzyme, a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate and a co-factor thereof.

48. The pharmaceutical composition of claim 29, wherein said agent includes a glutamate modifying enzyme, a co-factor thereof, a modified glutamate converting enzyme being selected incapable of converting said modified glutamate

into glutamate and a co-factor thereof.

49. The pharmaceutical composition of claim 29, wherein said agent includes a glutamate modifying enzyme, a co-factor thereof, and a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate.

50. The pharmaceutical composition of claim 29, wherein said agent includes a glutamate modifying enzyme, a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate and a co-factor thereof.

51. The pharmaceutical composition of claim 29, wherein said agent includes a glutamate modifying enzyme and a co-factor of a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate.

52. The pharmaceutical composition of claim 29, wherein said agent includes a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate and a co-factor thereof.

53. The pharmaceutical composition of claim 29, wherein said agent includes a co-factor of a glutamate modifying enzyme and a co-factor of a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate.

54. The pharmaceutical composition of claim 29, wherein said active ingredient is effective at a concentration not exceeding 1 g/Kg body weight/hour.

55. The pharmaceutical composition of claim 29, wherein said agent is at least one inhibitor of a glutamate synthesizing enzyme.

56. The pharmaceutical composition of claim 55, wherein said inhibitor is selected from the group consisting of gamma-Acetylenic GABA, GABAculine, L-canaline, 2-amino-4-(aminooxy)-n-butanoic acid, 3-Chloro-4-aminobutanoate, 3-Phenyl-4-aminobutanoate, Isonicotinic hydrazide;(S)-3-Amino-2-methylpropanoate, Phenylhydrazine; 4-Fluorophenyl)alanine, Adipate, Azaleic acid, Caproate, 3-Methylglutarate, Dimethylglutarate, Diethylglutarate, Pimelate, 2-Oxoglutamate, 3-Methyl-2-benzothiazolone hydrazone hydrochloride, Phenylpyruvate, 4-hydroxyphenylpyruvate, Prephenate and Indole pyruvate.

57. A pharmaceutical composition for reducing extracellular brain glutamate levels, the pharmaceutical composition comprising, as an active ingredient, pyruvate and oxaloacetate in a concentration suitable for reducing blood glutamate levels and a pharmaceutically acceptable carrier.

58. The pharmaceutical composition of claim 57, further comprising an enzymatic co-factor selected from the group consisting of NAD⁺, ADP, lipoic acid, lipoic acid precursor, pyridoxal phosphate, pyridoxal phosphate precursor leucine, thiamine pyrophosphate and thiamine pyrophosphate precursor.

59. The pharmaceutical composition of claim 57, wherein said concentration of pyruvate and oxaloacetate not exceeding 1 g/Kg body weight/hour.

60. Use of a blood glutamate level reducing agent for the manufacture of a medicament for the treatment and/or prevention of a medical condition associated with high extracellular brain glutamate levels, whereby reducing blood glutamate levels is beneficial.

61. The use of blood glutamate levels reducing agent of claim 60, wherein said medical condition is selected from the group consisting of brain anoxia, stroke, perinatal brain damage, traumatic brain injury, bacterial meningitis, subarachnoid hemorrhage, hemorrhagi shock, epilepsy, acute liver failure, glaucoma, amyotrophic lateral sclerosis, HIV, dementia, hemorrhagic shock, open heart surgery, aneurism

surgery, coronary artery bypass surgery grafting and Alzheimer's disease.

62. An article-of-manufacture comprising packaging material and a pharmaceutical composition identified for reducing extracellular brain glutamate levels being contained within said packaging material, said pharmaceutical composition including, as an active ingredient, an agent capable of reducing blood glutamate levels and a pharmaceutically acceptable carrier.

63. The article-of-manufacture of claim 62, wherein said agent is at least one glutamate modifying enzyme and/or a modification thereof.

64. The article-of-manufacture of claim 63, wherein said at least one glutamate modifying enzyme is selected from the group consisting of a transaminase, a dehydrogenase, a decarboxylase, a ligase, an aminomutase, a racemase and a transferase.

65. The article-of-manufacture of claim 64, wherein said transaminase is selected from the group consisting of glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, acetylornithine transaminase, ornithine-oxo-acid transaminase, succinyldiaminopimelate transaminase, 4-aminobutyrate transaminase, alanine transaminase, (s)-3-amino-2-methylpropionate transaminase, 4-hydroxyglutamate transaminase, diiodotyrosine transaminase, thyroid-hormone transaminase, tryptophan transaminase, diamine transaminase, cysteine transaminase, L-Lysine 6-transaminase, histidine transaminase, 2-aminoadipate transaminase, glycine transaminase, branched-chain-amino-acid transaminase, 5-aminovalerate transaminase, dihydroxyphenylalanine transaminase, tyrosine transaminase, phosphoserine transaminase, taurine transaminase, aromatic-amino-acid transaminase, aromatic-amino-acid-glyoxylate transaminase, leucine transaminase, 2-aminohexanoate transaminase, ornithine(lysine) transaminase, kynurenine-oxoglutarate transaminase, D-4-hydroxyphenylglycine transaminase, cysteine-conjugate transaminase, 2,5-diaminovalerate transaminase, histidinol-phosphate transaminase, diaminobutyrate-2-oxoglutarate transaminase, and udp-2-acetamido-4-

amino-2,4,6-trideoxyglucose transaminase.

66. The article-of-manufacture of claim 64, wherein said dehydrogenase is a glutamate dehydrogenase.

67. The article-of-manufacture of claim 64, wherein said decarboxylase is a glutamate decarboxylase.

68. The article-of-manufacture of claim 64, wherein said ligase is a glutamate-ethylamine ligase.

69. The article-of-manufacture of claim 64, wherein said transferase is selected from the group consisting of glutamate N-acetyltransferase and adenyltransferase.

70. The article-of-manufacture of claim 64, wherein said aminomutase is a glutamate-1-semialdehyde 2,1-aminomutase.

71. The article-of-manufacture of claim 62, wherein said agent is at least one co-factor of a glutamate modifying enzyme.

72. The article-of-manufacture of claim 71, wherein said co-factor is selected from the group consisting of oxaloacetate, pyruvate, NAD^+ , NADP^+ , 2-oxohexanedioic acid, 2-oxo-3-sulfopropionate, 2-oxo-3-sulfinopropionic acid, 2-oxo-3-phenylpropionic acid, 3-indole-2-oxopropionic acid, 3-(4-hydroxyphenyl)-2-oxopropionic acid, 4-methylsulfonyl-2-oxobutyric acid, 3-hydroxy-2-oxopropionic acid, 5-oxopentanoate, 6-oxo-hexanoate, glyoxalate, 4-oxobutanoate, α -ketoisocaproate, α -ketoisovalerate, α -keto- β -methylvalerate, succinic semialdehyde-(-4-oxobutyrate), pyridoxal phosphate, pyridoxal phosphate precursor and 3-oxoisobutanoate.

73. The article-of-manufacture of claim 62, wherein said agent is a

modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate and/or a modification thereof.

74. The article-of-manufacture of claim 73, wherein said modified glutamate converting enzyme is modified GOT.

75. The article-of-manufacture of claim 62, wherein said agent is a co-factor of a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate.

76. The article-of-manufacture of claim 75, wherein said agent is selected from the group consisting of lipoic acid, lipoic acid precursor, thiamine pyrophosphate, thiamine pyrophosphate precursor, pyridoxal phosphate and pyridoxal phosphate precursor.

77. The article-of-manufacture of claim 62, wherein said agent includes a glutamate modifying enzyme and a co-factor thereof.

78. The article-of-manufacture of claim 62, wherein said agent includes a glutamate modifying enzyme and a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate.

79. The article-of-manufacture of claim 62, wherein said agent includes a co-factor of a glutamate modifying enzyme and a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate.

80. The article-of-manufacture of claim 62, wherein said agent includes a co-factor of a glutamate modifying enzyme, a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate and a co-factor thereof.

81. The article-of-manufacture of claim 62, wherein said agent includes a glutamate modifying enzyme, a co-factor thereof, a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate and a co-factor thereof.

82. The article-of-manufacture of claim 62, wherein said agent includes a glutamate modifying enzyme, a co-factor thereof, and a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate.

83. The article-of-manufacture of claim 62, wherein said agent includes a glutamate modifying enzyme, a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate and a co-factor thereof.

84. The article-of-manufacture of claim 62, wherein said agent includes a glutamate modifying enzyme and a co-factor of a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate.

85. The article-of-manufacture of claim 62, wherein said agent includes a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate and a co-factor thereof.

86. The article-of-manufacture of claim 62, wherein said agent includes a co-factor of a glutamate modifying enzyme and a co-factor of a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate.

87. The article-of-manufacture of claim 62, wherein said active ingredient is effective at a concentration not exceeding 1 g/Kg body weight/hour.

88. The article-of-manufacture of claim 87, wherein said agent is at least one inhibitor of a glutamate synthesizing enzyme.

89. The article-of-manufacture of claim 88, wherein said inhibitor is selected from the group consisting of gamma-Acetylenic GABA, GABAculine, L-canaline, 2-amino-4-(aminooxy)-n-butanoic acid, 3-Chloro-4-aminobutanoate, 3-Phenyl-4-aminobutanoate, Isonicotinic hydrazide;(S)-3-Amino-2-methylpropanoate, Phenylhydrazine; 4-Fluorophenyl)alanine, Adipate, Azaleic acid, Caproate, 3-Methylglutarate, Dimethylglutarate, Diethylglutarate, Pimelate, 2-Oxoglutamate, 3-Methyl-2-benzothiazolone hydrazone hydrochloride, Phenylpyruvate, 4-hydroxyphenylpyruvate, Prephenate and Indole pyruvate.

90. A method of reducing extracellular brain glutamate levels in a subject in need thereof, the method comprising

- (a) obtaining a blood sample;
- (b) contacting said blood sample with an agent capable of reducing glutamate levels of cells present in said blood sample to thereby obtain glutamate depleted blood cells; and
- (c) introducing said glutamate depleted blood cells into the subject, thereby reducing extracellular brain glutamate levels thereof.

91. The method of claim 90, wherein said agent is at least one glutamate modifying enzyme and/or a modification thereof.

92. The method of claim 91, wherein said at least one glutamate modifying enzyme is selected from the group consisting of a transaminase, a dehydrogenase, a decarboxylase, a ligase, an aminomutase, a racemase and a transferase.

93. The method of claim 92, wherein said transaminase is selected from the group consisting of glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, acetylornithine transaminase, ornithine-oxo-acid transaminase,

succinyl-diaminopimelate transaminase, 4-aminobutyrate transaminase, alanine transaminase, (s)-3-amino-2-methylpropionate transaminase, 4-hydroxyglutamate transaminase, diiodotyrosine transaminase, thyroid-hormone transaminase, tryptophan transaminase, diamine transaminase, cysteine transaminase, L-Lysine 6-transaminase, histidine transaminase, 2-aminoadipate transaminase, glycine transaminase, branched-chain-amino-acid transaminase, 5-aminovalerate transaminase, dihydroxyphenylalanine transaminase, tyrosine transaminase, phosphoserine transaminase, taurine transaminase, aromatic-amino-acid transaminase, aromatic-amino-acid-glyoxylate transaminase, leucine transaminase, 2-aminohexanoate transaminase, ornithine(lysine) transaminase, kynurenine-oxoglutarate transaminase, D-4-hydroxyphenylglycine transaminase, cysteine-conjugate transaminase, 2,5-diaminovalerate transaminase, histidinol-phosphate transaminase, diaminobutyrate-2-oxoglutarate transaminase, and udp-2-acetamido-4-amino-2,4,6-trideoxyglucose.

94. The method of claim 92, wherein said dehydrogenase is a glutamate dehydrogenase.

95. The method of claim 92, wherein said decarboxylase is a glutamate decarboxylase.

96. The method of claim 92, wherein said ligase is a glutamate-ethylamine ligase.

97. The method of claim 92, wherein said transferase is selected from the group consisting of glutamate n-acetyltransferase and adenylyltransferase.

98. The method of claim 92, wherein said aminomutase is a glutamate-1-semialdehyde 2,1-aminomutase.

99. The method of claim 90, wherein said agent is at least one co-factor of a glutamate modifying enzyme.

100. The method of claim 99, wherein said co-factor is selected from the group consisting of oxaloacetate, pyruvate, NAD^+ , NADP^+ , 2-oxohexanedioic acid, 2-oxo-3-sulfopropionate, 2-oxo-3-sulfinopropionic acid, 2-oxo-3-phenylpropionic acid, 3-indole-2-oxopropionic acid, 3-(4-hydroxyphenyl)-2-oxopropionic acid, 4-methylsulfonyl-2-oxobutyric acid, 3-hydroxy-2-oxopropionic acid, 5-oxopentanoate, 6-oxo-hexanoate, glyoxalate, 4-oxobutanoate, α -ketoisocaproate, α -ketoisovalerate, α -keto- β -methylvalerate, succinic semialdehyde-(-4-oxobutyrate), pyridoxal phosphate, pyridoxal phosphate precursor and 3-oxoisobutanoate.

101. The method of claim 90, wherein said agent is a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate and/or a modification thereof.

102. The method of claim 101, wherein said modified glutamate converting enzyme is a modified GOT.

103. The method of claim 90, wherein said agent is a co-factor of a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate.

104. The method of claim 103, wherein said agent is selected from the group consisting of lipoic acid, lipoic acid precursor, thiamine pyrophosphate, thiamine pyrophosphate, pyridoxal phosphate and pyridoxal phosphate precursor.

105. The method of claim 90, wherein said agent includes a glutamate modifying enzyme and a co-factor thereof.

106. The method of claim 90, wherein said agent includes a glutamate modifying enzyme and a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate.

107. The method of claim 90, wherein said agent includes a co-factor of a

glutamate modifying enzyme and a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate.

108. The method of claim 90, wherein said agent includes a co-factor of a glutamate modifying enzyme, a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate and a co-factor thereof.

109. The method of claim 90, wherein said agent includes a glutamate modifying enzyme, a co-factor thereof, a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate and a co-factor thereof.

110. The method of claim 90, wherein said agent includes a glutamate modifying enzyme, a co-factor thereof, and a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate.

111. The method of claim 90, wherein said agent includes a glutamate modifying enzyme, a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate and a co-factor thereof.

112. The method of claim 90, wherein said agent includes a glutamate modifying enzyme and a co-factor of a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate.

113. The method of claim 90, wherein said agent includes a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate and a co-factor thereof.

114. The method of claim 90, wherein said agent includes a co-factor of a glutamate modifying enzyme and a co-factor of a modified glutamate converting enzyme being selected incapable of converting said modified glutamate into glutamate.

115. The method of claim 90, wherein said administering is effected at a concentration of said agent not exceeding 1 g/Kg body weight/hour.

116. The method of claim 90, wherein said obtaining the blood sample is effected from:

- (i) a matching blood type donor;
- (ii) a nonmatching blood type donor; and/or
- (iii) the subject in need thereof.

117. The method of claim 90, wherein said agent is at least one inhibitor of a glutamate synthesizing enzyme.

118. The article-of-manufacture of claim 117, wherein said inhibitor is selected from the group consisting of gamma-Acetylenic GABA, GABAculine, L-canaline, 2-amino-4-(aminooxy)-n-butanoic acid, 3-Chloro-4-aminobutanoate, 3-Phenyl-4-aminobutanoate, Isonicotinic hydrazide;(S)-3-Amino-2-methylpropanoate, Phenylhydrazine; 4-Fluorophenyl)alanine, Adipate, Azaleic acid, Caproate, 3-Methylglutarate, Dimethylglutarate, Diethylglutarate, Pimelate, 2-Oxoglutamate, 3-Methyl-2-benzothiazolone hydrazone hydrochloride, Phenylpyruvate, 4-hydroxyphenylpyruvate, Prephenate and Indole pyruvate.

119. A pharmaceutical composition for reducing extracellular brain glutamate levels, the pharmaceutical composition comprising, as an active ingredient, oxaloacetate diethylester capable of reducing blood glutamate levels and a pharmaceutically acceptable carrier.